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Cold Pain Threshold identifies a sub-group of patients with knee osteoarthritis that present with multi-modality hyperalgesia and elevated pain levels

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Abstract

Objectives: Cold hyperalgesia has been established as an important marker of pain severity in a number of conditions. This study aimed to establish the extent to which patients with knee OA demonstrate widespread cold, heat and pressure hyperalgesia. OA subjects with widespread cold hyperalgesia were compared to the remaining OA cohort to determine if they could be distinguished in terms of hyperalgesia, pain report, pain quality and physical function.

Methods: 80 subjects with knee OA and 40 matched healthy controls participated. OA participants completed a washout of their usual medication. Quantitative sensory testing (QST) was completed at three sites using standard methods. Cold and heat pain thresholds (CPT, HPT) were tested using a Peltier thermode and pressure pain thresholds (PPT) using a digital algometer. All subjects completed the SF-36 questionnaire and OA subjects completed the PainDETECT, WOMAC and PQAS questionnaires.

Results: OA subjects demonstrated widespread cold hyperalgesia ($p<0.0001$), had lower PPT at the index knee ($p<0.0001$) compared to controls and reported decreased physical health on the SF-36 ($p=0.01$). The OA sub-cohort with high global CPT (≥12.25°C) exhibited multi-modality sensitization compared to the remaining OA cohort (PPT $p<0.0001$, CPT $p<0.0001$, HPT $p=0.021$ Index knee). This group also reported increased pain, decreased function and more features of neuropathic pain.

Discussion: This study identified a specific sub-group of patients with knee OA who exhibited widespread, multi-modality hyperalgesia, more pain, more features of neuropathic pain and greater functional impairment. Identification of patients with this pain phenotype may permit more targeted and effective pain management.

(250 words)

Keywords

Cold hyperalgesia, neuropathic pain, knee osteoarthritis, multi-modality hyperalgesia, central sensitisation

Introduction

Osteoarthritis (OA) is a common arthritic disorder [1, 2] often associated with pain and local tenderness or pressure hyperalgesia around the affected joint(s) [3, 4]. Although knee OA has been considered the archetypal model of non-inflammatory or nociceptive pain [5] it is now recognised that some patients with knee OA also exhibit features of neuropathic pain [6], which may be associated with sensory deficits and widespread multi-modality hyperalgesia [7].

Local and widespread pressure hyperalgesia is well established in patients with knee osteoarthritis, including evidence of pressure hyperalgesia at the contralateral knee or at sites in the upper or lower limb [4, 5, 7-10]. Research evaluating thermal hyperalgesia in this patient cohort is more limited. Cold and heat hyperalgesia has been demonstrated in hip osteoarthritis [3] and we have recently demonstrated widespread cold and pressure hyperalgesia in a pilot study in patients with knee OA [9] but no difference between OA and control subjects in cold or heat pain thresholds across three test sites was reported in one study evaluating knee OA [5]. Wylde et al. [7] reported no difference in heat pain threshold but did not analyze cold pain threshold data due to technical issues with their thermode measurement. Therefore, while there is considerable evidence that local and widespread pressure hyperalgesia is a common feature in people with painful knee OA, the potential importance of heat and cold hyperalgesia has yet to be fully established.

Studies evaluating quantitative sensory testing (QST) data in other chronic musculoskeletal disorders suggest that pressure and cold hyperalgesia may co-present, for example in tennis elbow [11-13], spinal pain [14, 15], fibromyalgia [16], temporomandibular joint disorder [17] and whiplash associated disorder (WAD) [18]. An association between pain severity and chronicity and the presence of cold hyperalgesia has been suggested in WAD [19] and tennis elbow [20]. Based on the findings of systematic reviews, the presence of cold hyperalgesia

has been proposed as a major prognostic factor in the development of increased central sensitisation [21] and long term pain and disability in WAD [22, 23]. The presence of cold evoked pain is also recognized as an important feature in neuropathic pain states [24, 25] and has been linked to the presence of neuropathic pain following whiplash injury [26]. In combination, these findings indicate the value of identifying whether cold hyperalgesia is present alongside pressure hyperalgesia and heat hyperalgesia as these features may be linked to increased pain severity, greater functional impairment and also potentially to the development of neuropathic pain.

The current study investigated the extent to which widespread cold, pressure and heat hyperalgesia is experienced by subjects with knee OA, compared with healthy controls. The study also tested sensory detection thresholds to determine if any sensory deficits were present. Z-score analysis was used to identify a sub-cohort of knee OA subjects who exhibited widespread cold hyperalgesia. This sub-cohort was compared to the remaining OA subjects to determine differences in QST measures, levels of pain, pain characteristics and perceived function.

Methods

Participants

Eighty participants with painful knee OA and 40 pain-free healthy control subjects were recruited from the Perth community. Volunteers with painful knee OA (visual analogue scale score ≥3 of 10) were recruited and assessed for suitability by a Rheumatologist, using the American College of Rheumatology classification system [27]. Exclusion criteria included: history of systemic inflammatory conditions; neurological disorders affecting sensory or motor function; recent (<6 months) lower limb injury or surgery; or history of other chronic pain disorders (e.g. Fibromyalgia). Healthy pain-free volunteers were included if aged 50 years or more, in good general health and with no current pain or history of OA.

All participants provided written informed consent before participating in the study. Ethical approval was provided by Royal Perth Hospital Medical Research Ethics Committee (Approval EC2009/100) and by Curtin University Human Research Ethics Committee (Approval HR26/2010).

Study Design

The study used a cross-sectional design, with subjects attending the laboratory at Royal Perth Hospital for one test session. Participants with OA underwent a washout period equal to five half lives of their analgesic or NSAID medication before testing. They were able to use paracetamol for analgesia if required but were asked to refrain from its use for 12 hours before testing. All subjects completed the Short from health survey (SF-36) quality of Life questionnaire [28]. Participants with knee OA also completed the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index for the Knee [29], the PainDETECT questionnaire [30] and the Pain Quality Assessment Scale (PQAS) [31]. All participants then completed quantitative sensory testing measures. Order of testing was randomized between QST modalities, although for heat and cold stimuli, detection threshold was always tested before pain threshold.

Quantitative Sensory Tests

All quantitative sensory tests were applied in triplicate using standardized instructions at standardized sites: at the OA knee and the contralateral knee (medial joint line) and at the ipsilateral elbow over the extensor carpi radialis brevis (ECRB) muscle [32].

Pressure Pain Threshold (PPT) was assessed using an electronic digital pressure algometer (Somedic AB, Sweden), a device that has consistently shown good reliability [33]. A 1cm² algometer probe was applied at 90° to the skin at a rate of 40kPa/sec. Subjects were

instructed to depress the hand-held switch as soon as the sensation of pressure became one of painful pressure [34]. Lower PPT values indicated increased sensitivity.

Cold Detection and Cold Pain Thresholds (CDT & CPT) were measured using a Peltier thermode (Medoc, Israel) and standard Method of Limits [35]. The probe was attached to the test site with a Velcro™ strap. The temperature reduced at a rate of 1°C/sec from a baseline temperature of 32°C to a minimum of 0°C. Detection threshold (CDT) was always measured first. Participants were instructed to depress the hand-held switch as soon as they perceived any cooling change from baseline. For cold pain threshold, participants were instructed to press the switch as soon as the cooling sensation changed to one of painful cold. Some subjects failed to indicate cold pain before the thermode reached the minimum temperature of 0°C. These participants were assigned a cold pain threshold of 0°C. Elevated CPT values indicated increased sensitivity.

Warm Detection and Heat Pain Thresholds (WDT & HPT) were measured with the Medoc Peltier thermode using similar methodology to cold testing (baseline 32°C, 1°C/sec ascending ramp), with maximum temperature set at 50°C. WDT was defined as the temperature (°C) at which participants first perceived an increase in warmth from baseline, whilst HPT was defined as the temperature (°C) at which participants perceived that the heating sensation had become one of painful heat. Some subjects failed to indicate heat pain before the thermode reached the maximum temperature of 50°C. These participants were assigned a heat pain threshold of 50°C. Lower HPT values indicated increased sensitivity.

Self-Report Questionnaires

SF-36. Quality of Life was evaluated with the SF-36v2, which has demonstrated good validity and reliability for a range of conditions and for healthy subjects [28]**.** The tool measures the self-perceived impact of health status on quality of life via eight domains, using

Likert-type response categories. The current study calculated the physical and mental health sub-scales for analysis.

WOMAC was used to evaluate subjective pain, stiffness and functional limitation for OA subjects. This OA-specific self-report scale has been widely used to measure pain and disability from knee OA, demonstrating good internal validity and test-retest reliability [29].

PainDETECT is a validated self-report tool that has been used to identify neuropathic pain features in a range of conditions [30]. The questionnaire uses a combination of VAS scale, body diagram and Likert-type questions to ask about everyday frequency of symptoms such as 'electric shocks' or painful light touch. A total score is calculated, with subjects scoring less than 13/35 classified as 'negative neuropathic' and 19+ as 'positive neuropathic'.

PQAS was also used to provide data regarding the type of spontaneous pain experienced by OA subjects [31]. The questionnaire includes 17 questions about the type of pain plus additional numerical rating scales for unpleasantness and surface versus deep pain. Three specific pain sub-scores are then calculated [31]: paroxysmal, surface and deep. It has been suggested that differences between the deep and surface or paroxysmal subscales may differentiate nociceptive-type and neuropathic-type pain [31].

Statistical Analysis

Data were analyzed using SPSS version 20 (IBM Corp) with Alpha set at $p<0.05$. The data were analyzed in two stages. Initial comparisons were carried out between the OA and control groups. Kolmogorov-Smirnov tests determined that the QST and PQAS data were not normally distributed and so non-parametric tests (Mann-Witney U-test, Kruskal-Wallis test) were applied. WOMAC, PainDETECT and SF-36 data met the assumption of normality based on the Kolmogorov-Smirnov test and so were analyzed using parametric tests (t-test, One-way ANOVA).

Based on a previous study it was predicted that 20-30% subjects would present with elevated cold pain thresholds, potentially associated with more severe pain [9]. With an estimated sample size of n=20 for the elevated cold pain threshold group, it was calculated that the study would have 80% power to detect a between-groups mean difference of 38kPa (SD 57kPa) in PPT, a 5.4˚C (SD 2.3˚C) difference in CPT and a 7.8 mm (SD 16mm) difference in total WOMAC score [9]. These values equate to a 15-20% between group difference [9]. Based on the elevated CPT group constituting 25% of the overall cohort a sample of 80 subjects with knee OA was recruited for the study.

Following initial comparisons and using the approach suggested by the German Research Network on Neuropathic Pain (DFNS) [36], Z-scores for all measures were calculated for individual subjects with knee OA using the mean and standard deviation data from the pain-free control group. Data for cold and heat measures were converted to difference values from the baseline temperature of 32°C. All data were log transformed and the Z-score calculated using the following formula:

$$Z\ score = \frac{(X\ \text{Subject} - \text{Mean Painfree controls})}{\text{SD Painfree controls}}$$

OA subjects with Z-scores outside the 95% confidence interval of the mean of the pain-free control group (Z-score < -1.96 or > 1.96) were identified and classified as abnormal. The percentage of abnormal subjects in the OA group for each measure at each site was calculated [7].

A global CPT value (mean of all sites) was calculated and Z-scores determined. This identified that 35 out of 80 participants with OA exhibited a global CPT value that was at

least one Z-score higher than the control group mean. This indicates greater cold pain sensitivity. This high CPT (increased cold pain sensitivity) OA group was then compared to the remaining OA cohort and the pain-free control group using parametric and non-parametric tests as appropriate. Correlations between global CPT and other key variables were also evaluated.

Results

Subject demographics

The OA cohort comprised 80 participants (36 male: 44 female) with a mean age of 64 years (range 50-86 years). Mean BMI was in the overweight category, with 38% subjects categorized as obese. They reported moderate pain (WOMAC Pain 18.5/50) and functional disability (WOMAC function 53.4/250). Two thirds of the OA participants reported regular use of at least one analgesic medication: slow release high dose paracetamol ("Panadol Osteo") (40%) or NSAIDs (36%). Two subjects reported opioid use. The participants self-reported their most painful knee which was defined as the index knee.

The pain-free cohort of 40 subjects (16 male: 24 female) had a similar mean age of 64 years (range 50-81 years), mean BMI in the overweight category but only 10% classified as obese.

Comparisons between the OA and pain-free groups

Pressure pain thresholds (OA Vs Control)

OA participants had lower mean PPT than the pain-free controls at the index knee ($P<0.0001$) (Figure 1) but there was no significant difference in mean PPT values at the contralateral knee or the ECRB sites. Z-score analysis showed that 22.50% of OA subjects exhibited pressure hyperalgesia at the index knee, 16.25% at the contralateral knee and 3.75% at the ECRB site (Figure 2).

Cold detection and pain thresholds (OA Vs Control)

OA participants had significantly reduced CDT at the index knee (p=0.008) and contralateral knee (p=0.027) but not at the ECRB site (p=0.132) (Figure 3). Cold pain thresholds were significantly higher at all sites (p<0.0001) in the OA group compared to the pain-free group (Figure 4). Z-Score analysis: 11.25% of OA participants had cold hypoesthesia at the index knee, 17.50% at the contralateral knee and 17.50% at the ECRB site. Cold hyperalgesia was present in a large percentage of OA subjects with 47.5% of participants exhibiting abnormal CPT at the index knee, 37.5% at the contralateral knee and 43.75% at the ECRB sites (Figure 2).

Warm detection and heat pain thresholds (OA Vs Control)

Warm detection thresholds were significantly elevated at the index knee (p=0.01), contralateral knee (p=0.022) and ECRB sites (p=0.033) (Figure 5). However, there was no significant difference in HPT (Figure 6) at any site (index knee p=0.956, contralateral knee p=0.824, ECRB p=0.486). 8.75% of OA participants had heat hypoesthesia at the index knee, 11.25% at the unaffected knee and 7.50% at the ECRB sites (Z-Score analysis). 10% of participants in the OA group exhibited heat hyperalgesia at the index knee with 15% and 13.75% at the unaffected knee and ECRB site respectively (Figure 2).

SF-36 (OA Vs Control)

Participants with knee OA exhibited reduced scores on the physical health sub-scale of the SF-36 (p=0.01) but were not significantly different on the mental health sub-scale (p=0.513) compared to pain free controls.

Comparison between the cold hyperalgesic and non-hyperalgesic OA sub-groups

Following Z-score analysis of global CPT values 43.75% of the OA cohort were classified as cold hyperalgesic, equating to a CPT cut-off ≥12.25°C. This group had elevated cold pain thresholds indicative of increased cold pain sensitivity. The OA cohort was therefore divided

into a high CPT group (n=35) and a low CPT group (n=55). Comparisons were then made between these two OA sub-groups and the control group across the range of measures.

Pressure pain thresholds (High CPT Vs Low CPT Vs Control)

The Kruskal-Wallis test showed there was a significant difference in PPT at all sites ($p<0.0001$). Between group comparisons (Mann-Witney U) showed a significant difference in PPT between the high CPT and low CPT OA groups at all sites ($p<0.0001$: Figure 1) with the cold hyperalgesic OA group exhibiting greater pressure hyperalgesia. The cold hyperalgesic group also exhibited greater pressure hyperalgesia than the pain-free control group at the index knee ($p<0.0001$) and contralateral knee ($p<0.0001$) but no significant difference at the ECRB site ($p=0.329$) (Figure 1).

Cold detection and pain thresholds (High CPT Vs Low CPT vs Control)

There was a significant difference between groups in CDT (Kruskal-Wallis) at all sites (OA knee $p<0.0001$, contralateral knee $p=0.001$, ECRB $p<0.0001$). Between-group comparisons (Mann-Witney U) showed the low CPT OA group exhibited significantly reduced cold detection thresholds, indicative of impaired cold perception at all sites (index knee $p=0.001$, contralateral knee $p=0.002$, ECRB $p=0.0001$) (Figure 3). However, there were no significant differences in CDT between the cold hyperalgesic OA group and the control group (index knee $p=0.467$, contralateral knee $p=0.853$, ECRB $p=0.161$). The Kruskal-Wallis test was significant at all sites for CPT ($p<0.0001$). Between-group comparisons showed differences in CPT ($p<0.0001$) between the high CPT and low CPT OA groups at all sites (Figure 4) and also between the cold hyperalgesic group and the control group ($p<0.0001$) at all sites. No significant difference was seen between the low CPT group and the control group.

Warm detection and heat pain thresholds (High CPT Vs Low CPT Vs Control)

There was a significant group difference in WDT at the index knee ($p=0.015$) and ECRB sites ($p=0.022$) but not at the contralateral knee ($p=0.073$). Between-groups comparison showed

no significant differences in WDT between the two OA sub-groups (index knee p=0.168, contralateral knee p=0.961, ECRB p=0.082). A significant difference in WDT existed between the cold hyperalgesic OA group and the control group at the contralateral knee (p=0.046) but not at the other sites (index knee p=0.137, ECRB p=0.410) (Figure 5). HPT was significantly different between groups at all sites (index knee p=0.021, contralateral knee p=0.037, ECRB p=0.01), Between-groups comparison showed that the cold hyperalgesic OA group exhibited greater heat hyperalgesia at all sites (index knee p=0.007, contralateral knee p=0.017, ECRB p=0.005) (Figure 6) compared to the remaining OA participants although HPT did not differ between the cold hyperalgesic group and the control group at any site (index knee p=0.098, contralateral knee p=0.08, ECRB p=0.216).

SF-36 (High CPT Vs Low CPT Vs Control)

There was a significant difference between groups for the SF-36 physical health sub-scale ($F_{2,117}$= 4.649, P=0.011). Cold hyperalgesic OA participants had significantly reduced scores on the SF-36 physical health sub-scale compared to the pain-free group (p=0.006), although not compared to the remaining OA subjects (p=0.093). There was no difference in mental health sub-scale score ($F_{2,117}$=0.140, P=0.87) between the three groups.

WOMAC (High CPT Vs Low CPT)

OA participants with elevated cold pain thresholds also reported significantly greater pain and more impaired function than the remaining cohort: WOMAC pain (p=0.014); WOMAC function (p=0.032), however there was no difference in WOMAC stiffness score (p=0.46) (Figure 7).

PainDETECT and PQAS (High CPT Vs Low CPT)

The high CPT OA sub-group exhibited more features of neuropathic pain, reporting significantly higher PainDETECT scores (p<0.0001) (Figure 7) and higher scores for PQAS

surface (p=0.017) and paradoxical (p=0.045) pain sub-scores but no difference in the PQAS deep pain sub-score (p=0.297) compared to the low CPT OA group (Figure 7).

Correlations between Global CPT and other key variables

The Global mean CPT measure showed significant correlations with PPT (r=-0.533, P=0.0001), CPT (r=0.893, P=0.0001) and HPT (r=-0.398, P=0.0002) at the index knee as well as well as PainDETECT score 0.566, P=0.0001), WOMAC Pain (r=0.323, P=0.003) and function (r=0.240, P= 0.032) scores and SF-35 Physical health sub score (r=-0.273, P=0.014). Global mean CPT was not correlated with ALF score (r=0.209, P=0.063), WOMAC stiffness (r=0.117, P=0.30) and SF-36 mental health subscore (r=-0.086, P=0.449).

Discussion

Findings

Compared with pain-free controls, a cohort of 80 individuals with knee OA exhibited signs of widespread cold hyperalgesia, pressure hyperalgesia at the index knee and no evidence of heat hyperalgesia. When individuals with OA were divided into high and low CPT groups according to normalized Z-scores, there was clear differentiation, with the high CPT (cold hyperalgesic) sub-group showing widespread hyperalgesia to pressure and to thermal modalities compared with the remaining OA cohort. Importantly, the cold hyperalgesic group also reported higher pain levels, more reduced function and increased features of neuropathic-type pain, as compared with the low CPT group whose pain appeared to be more limited and nociceptive in quality. Interestingly, there was no difference in the scores for the mental health subscale of the SF-36 between any of the groups, suggesting that while the high CPT experienced more pain and functional limitation they did not appear to experience significantly elevated psychological distress. A single measure of global cold pain threshold clearly differentiated two OA sub-groups: one with modest pain and modest self-reported functional impairment and another with more widespread multi-modality hyperalgesia, much

greater levels of pain and dysfunction and more evidence of neuropathic-type pain. Further research is clearly warranted to determine if the presence of an elevated cold pain threshold is a useful prognostic indicator in patients with knee OA, as has been found with WAD and Tennis elbow [20, 22].

Our study confirmed previous research by demonstrating the presence of pressure hyperalgesia around the index knee in patients with OA. Although the cold hyperalgesic sub-group showed some evidence of pressure hyperalgesia in the contralateral knee, evidence of widespread pressure hyperalgesia across the whole OA cohort was not seen, with no indication of any difference at the upper limb ECRB site. This contrasts with our previous findings [9] and the findings of Wylde et al [7] and Harden et al [5] who demonstrated the presence of pressure hyperalgesia at upper limb test sites. Further research is required to determine the extent to which widespread pressure hyperalgesia might vary in the total OA cohort.

There were however clear differences in cold pain thresholds at all sites, indicating widespread cold hyperalgesia in the OA cohort. Our finding that a substantial proportion of OA participants (between 37.5% and 47.5%) exhibited cold hyperalgesia based on Z-scores has not previously been reported. Given the importance of elevated cold pain thresholds as an indicator of pain severity and chronicity in other conditions [19, 20, 22] this is a very important finding that has potential clinical implications for prognosis and warrants further investigation in OA.

There were no significant differences in heat pain thresholds between the knee OA and pain-free control groups, reflecting previous studies in OA [5, 7] and Tennis Elbow [11, 37]. However, the study found significantly increased HPT in the cold hyperalgesic sub-group compared with both the remaining OA cohort and the control group, suggesting there is a substantial sub-group of people with knee OA who experience widespread heat hyperalgesia.

This is also reflected in the 10% and 15% of subjects who had HPTs more than one Z-score less than the control group mean. Our study is the first to identify a sub-group of OA sufferers with widespread, multi-modality hyperalgesia to heat, cold and pressure. This may be an important marker of central sensitization in this cohort.

Consistent differences in cold and warmth detection thresholds existed between the OA and control groups at each test site. Subjects with knee OA exhibited elevated WDTs and reduced CDTs, reflecting impaired detection of both heat and cold. These findings were present at all test sites, perhaps suggestive of widespread sensory impairment. The impaired warmth detection seemed to be a feature of the entire OA cohort since there were no differences between the high and low CPT groups. In contrast, the difference in CDT appears to be predominantly driven by the low CPT (non cold hyperalgesic) group who demonstrated impaired cold detection compared with the cold hyperalgesic group. It might be thought that the cold hyperalgesic OA group was simply hypersensitive to all cold sensation, however their mean cold detection thresholds were not significantly different to the control group. This therefore suggests that the OA subjects with the greatest sensory impairment were not those exhibiting the greatest sensitization. It should be acknowledged that multiple comparisons increase the risk of Type 1 error for some of these measures. The presence of sensory impairments in patients with OA has been identified and requires further investigation.

Implications for research and clinical practice

The OA sub-group with cold hyperalgesia demonstrated widespread pressure hyperalgesia, similar to previous studies [5, 7, 9] but also widespread thermal hyperalgesia. This widespread multi-modality hyperalgesia (pressure, heat, cold) may be indicative of increased central sensitization [21, 38]. The cold hyperalgesic sub-group also had elevated pain and dysfunction scores on the WOMAC questionnaire although no difference in stiffness scores. This would suggest that they were experiencing greater pain severity and more functional

limitation than the remaining OA cohort. This sub- group also had significantly elevated scores on PainDETECT and on the surface and paradoxical components of PQAS, although not on the deep component, suggesting that they also exhibited more features of neuropathic pain than the remaining OA cohort. It must be noted that mean PainDETECT score for the cold hyperalgesic sub-group was 14.97, which is in the unclear category (13-18) rather than the positive neuropathic category (19+), meaning that this group would not meet established criteria for a neuropathic pain classification [39]. A number of previous studies have identified a sub cohort of people with knee OA who have elevated scores on the PainDETECT questionnaire, placing them in the positive neuropathic category [6, 40-42]. It remains an open question as to whether people with knee OA can be classified as having probable or definite neuropathic pain [39]. It has been suggested that elevated PainDETECT scores may be more reflective of centrally augmented pain rather than the presence of identifiable neuropathic pain [42].

Overall therefore, there were differences between the OA CPT sub-groups in multi-modality hyperalgesia, pain report, neuropathic pain features and perceived physical function, suggesting that the presence of cold hyperalgesia identifies a group with a more severe pain presentation. The suggestion that these people may be experiencing some degree of neuropathic pain has to be tempered by the fact that they exhibit only minor evidence of sensory deficit in warm detection thresholds. The additional pain sensitivity they exhibit may be reflective of more extensive sensitization within the nervous system and significant central augmentation of pain. It is apparent from this study that many of the differences in pain sensitivity between OA and pain-free cohorts are driven by a sub-group of less than 50% of subjects, with the remaining OA subjects exhibiting pain thresholds very similar to normal, painfree individuals. Future studies would therefore benefit from including CPT measures and determining the percentage of participants with multi-modality hyperalgesia in any OA

cohort. A recent study [43] demonstrated that patients with ongoing pain one year after total knee arthroplasty exhibit many similar features to the cold hyperalgesic cohort in this study including the presence of cold hyperalgesia, suggesting that this might be a potential indicator of poor outcomes following surgery. Evaluation of cold pain thresholds and identification of this sub-group in future intervention studies could provide valuable prognostic information that could help to determine if they have an increased likelihood of poor treatment outcomes following pharmacological, physical or surgical treatments. Elevated cold pain thresholds have been identified as an important prognostic indicator for WAD and Tennis Elbow and this measure may be of similar value in OA.

Conclusion

This study identified a substantial sub-group of patients with knee OA who exhibited marked cold hyperalgesia. These individuals demonstrated widespread, multi-modality hyperalgesia for cold, heat and pressure stimuli suggesting significant sensitization of their nociceptive systems. They reported more pain, more features of neuropathic pain and greater functional impairment than the remaining OA group.

(3,963 words)

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Figure Legends

Figure 1. Pressure pain thresholds at each of the three test sites. There was a significant difference in PPT between the OA and control groups at the index knee (Panel A). There was a significant difference in PPT between the low CPT and high CPT groups at all sites (Panels A-C) and there was a significant difference between the high CPT and control group PPT measures at the index knee and the contralateral knee (Panels A and B).

Figure 2. Percentages of OA subjects with test values more than one Z-score higher or lower than the 95% confidence interval of the mean value for the control group. Values that indicate hyperalgesia are presented as positive scores. Values that indicate hypoesthesia are presented as negative scores.

Figure 3. Cold detection thresholds at each of the three test sites. There was a significant difference in CDT between the OA and control groups at the index knee and the contralateral knee (Panels A and B). There was also a significant difference in CDT between the high and low CPT groups at all sites (Panels A-C).

Figure 4. Cold pain thresholds at each of the three test sites. There was a significant difference in CPT between the OA and control groups at all sites (Panels A-C). There was also a significant difference in CPT between the low CPT and high CPT groups at all sites (Panels A-C) and there was a significant difference between the high CPT and control group CPT measures at all sites (Panels A-C).

Figure 5. Warm detection thresholds at each of the three test sites. There was a significant difference in WDT between the high CPT group and the control group at the contralateral knee (Panel B). There was also a significant difference in WDT between the OA and control groups at all sites (Panels A-C).

Figure 6. Heat pain thresholds at each of the three test sites. There was a significant difference in HPT between the low CPT and high CPT groups at all sites (Panels A-C).

Figure 7. Comparison between low and high CPT groups for scores obtained for the WOMAC, PainDETECT and PQAS (Mean ± SD) questionnaires.

Figure

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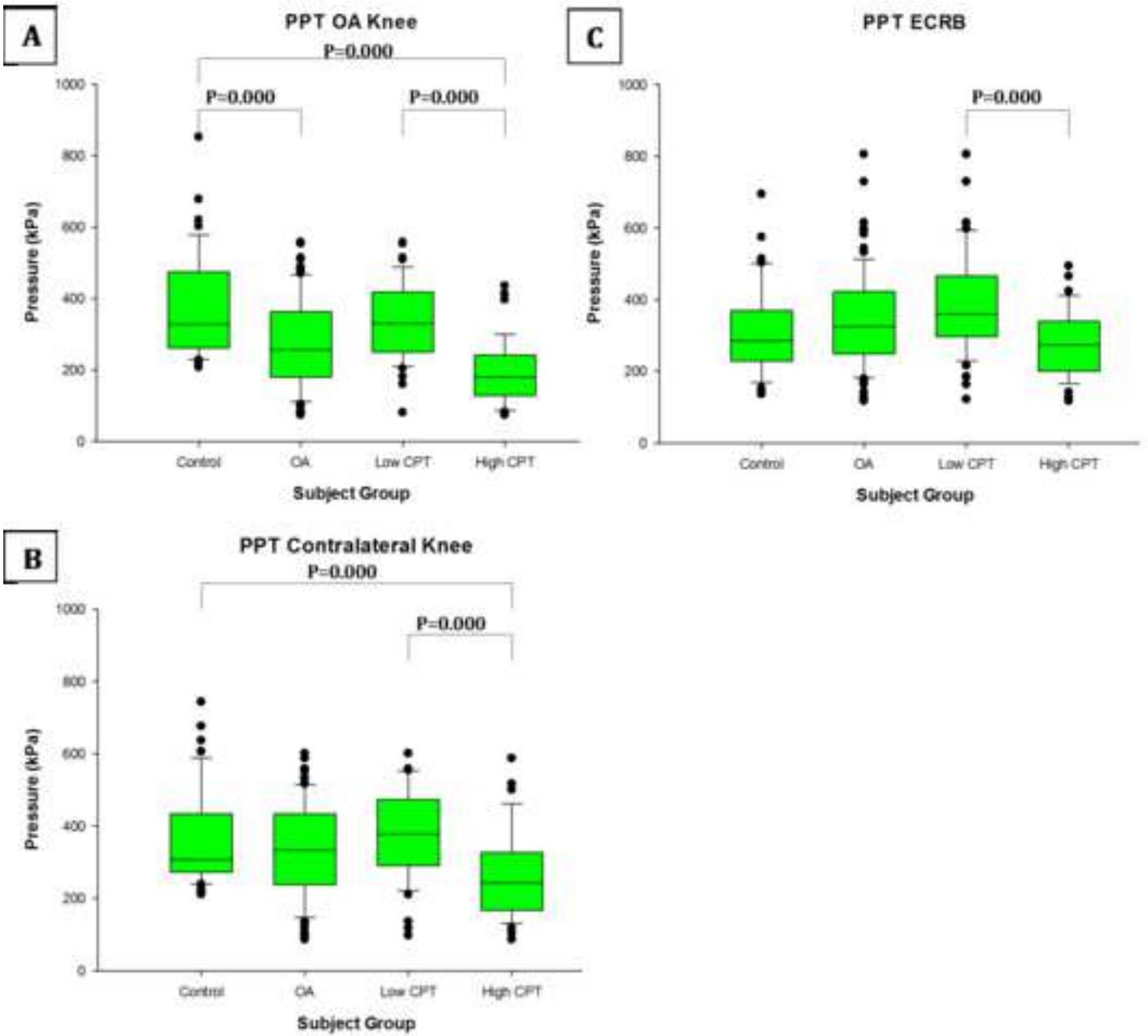

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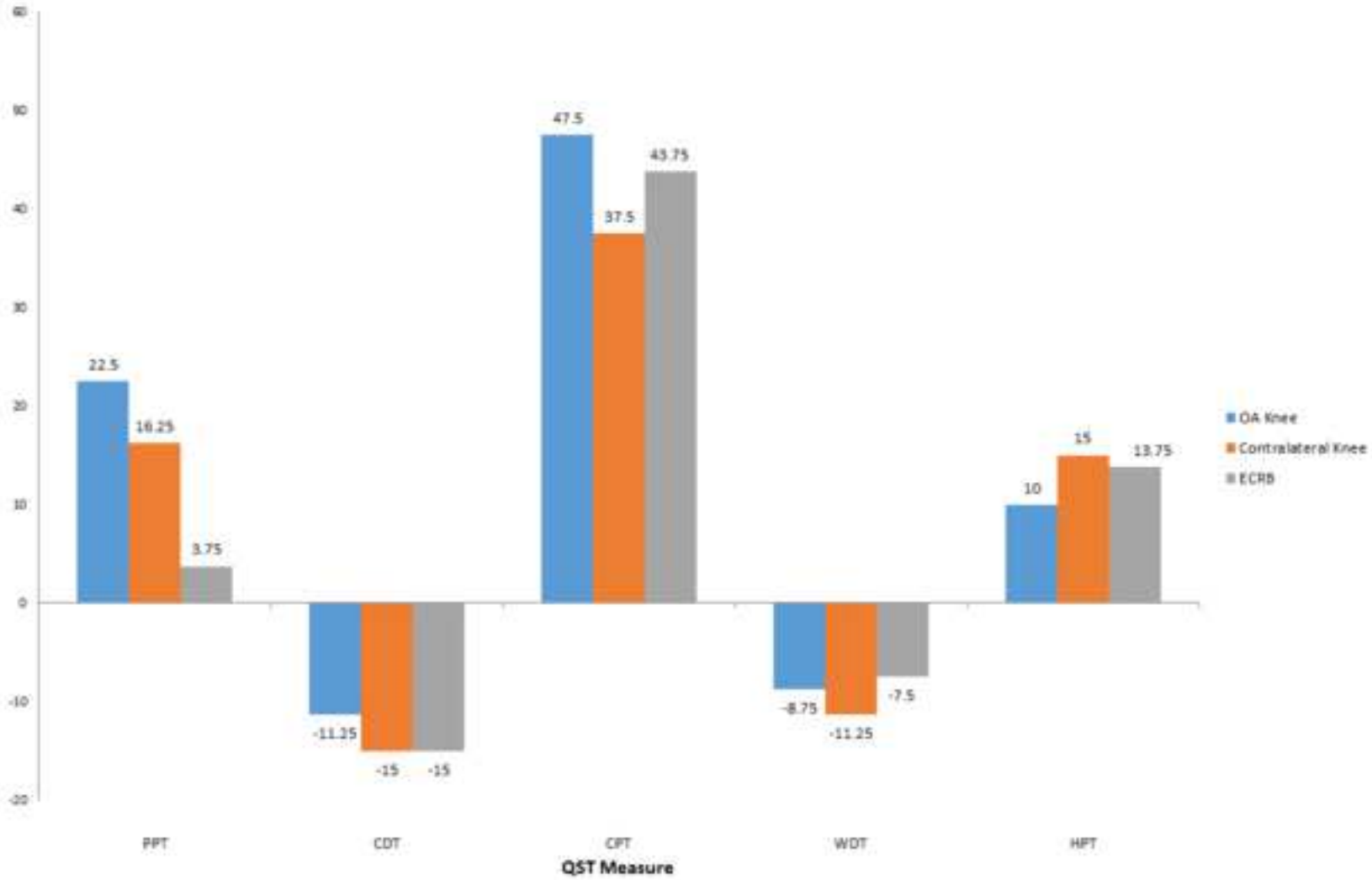

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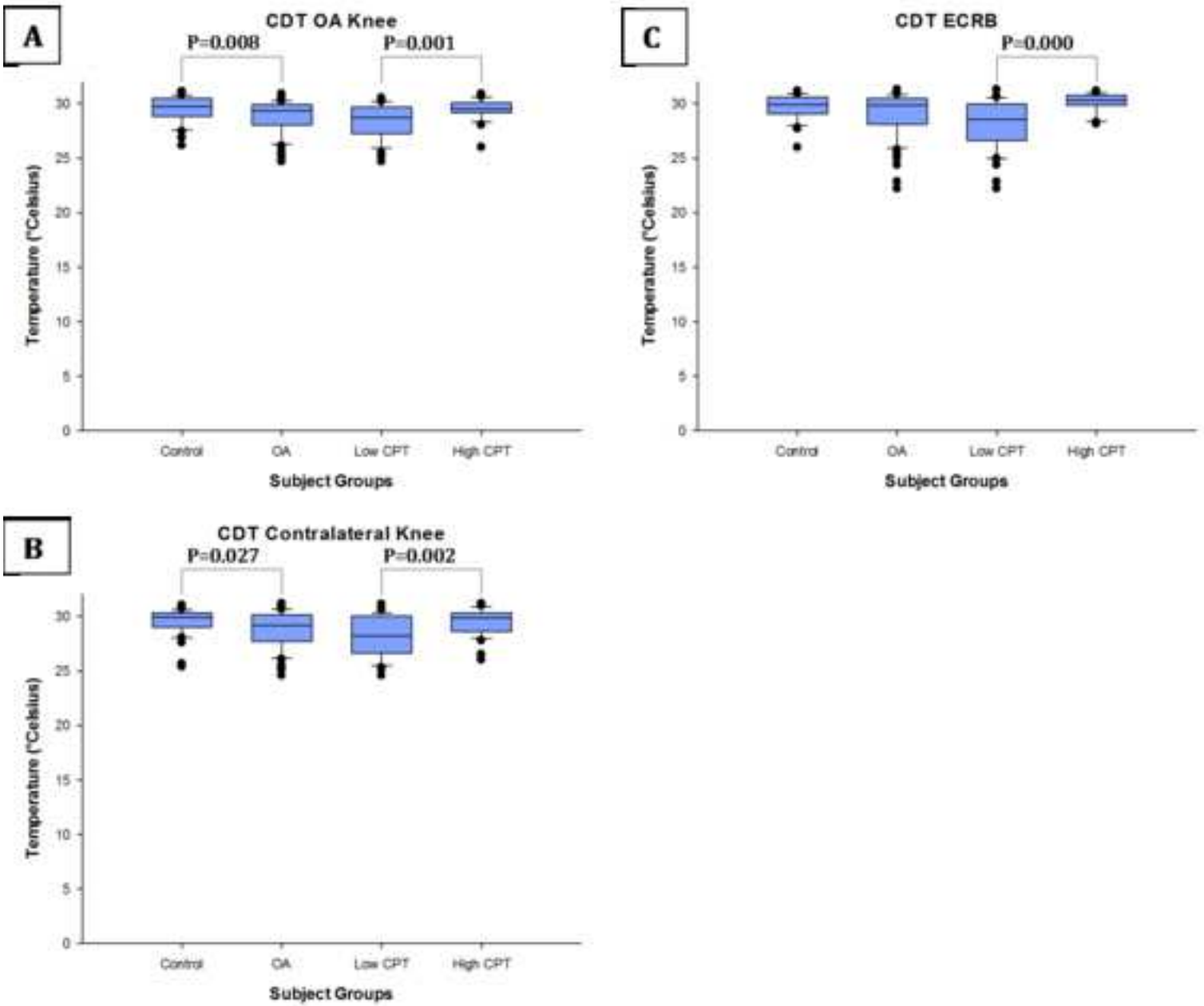

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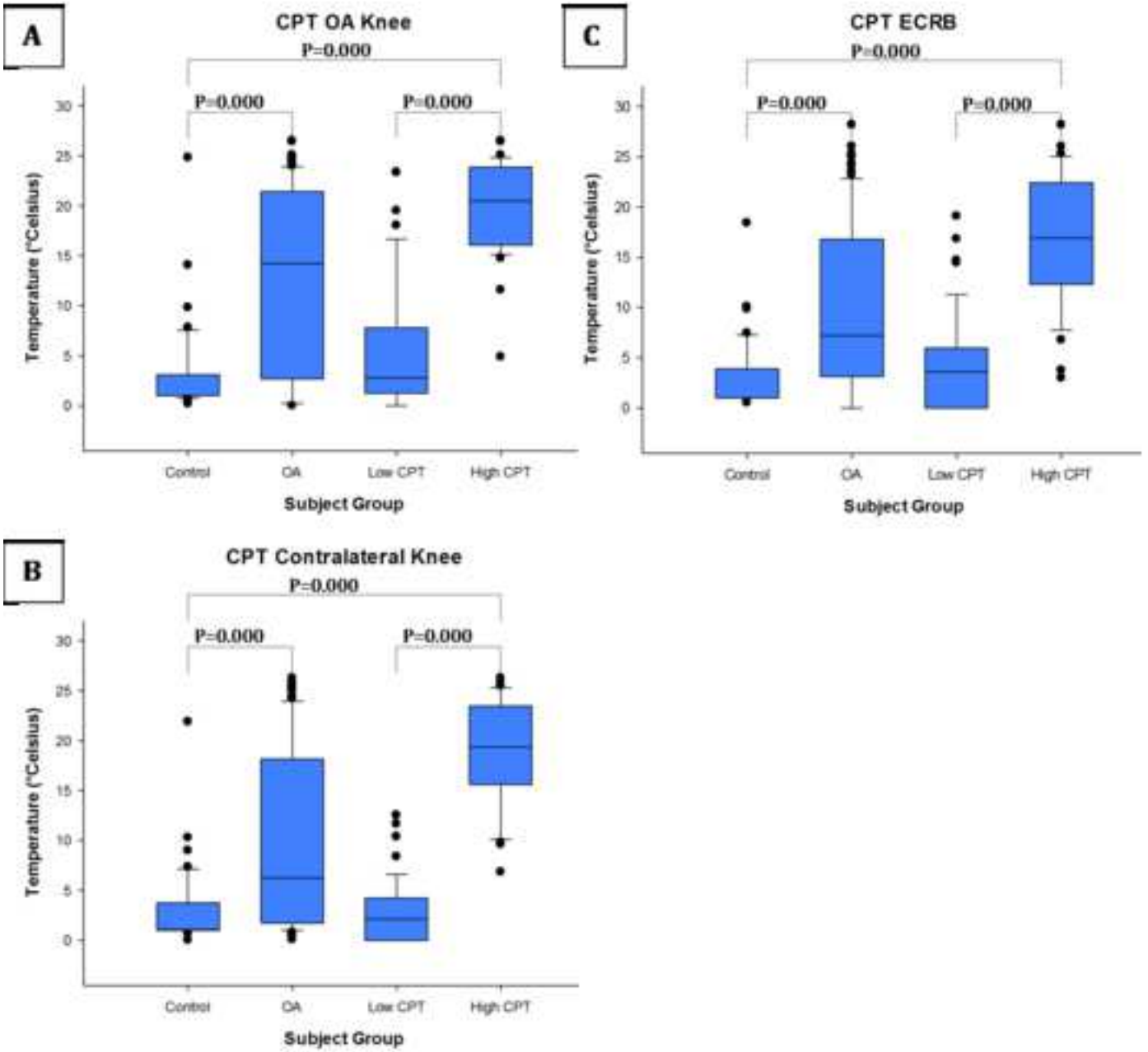

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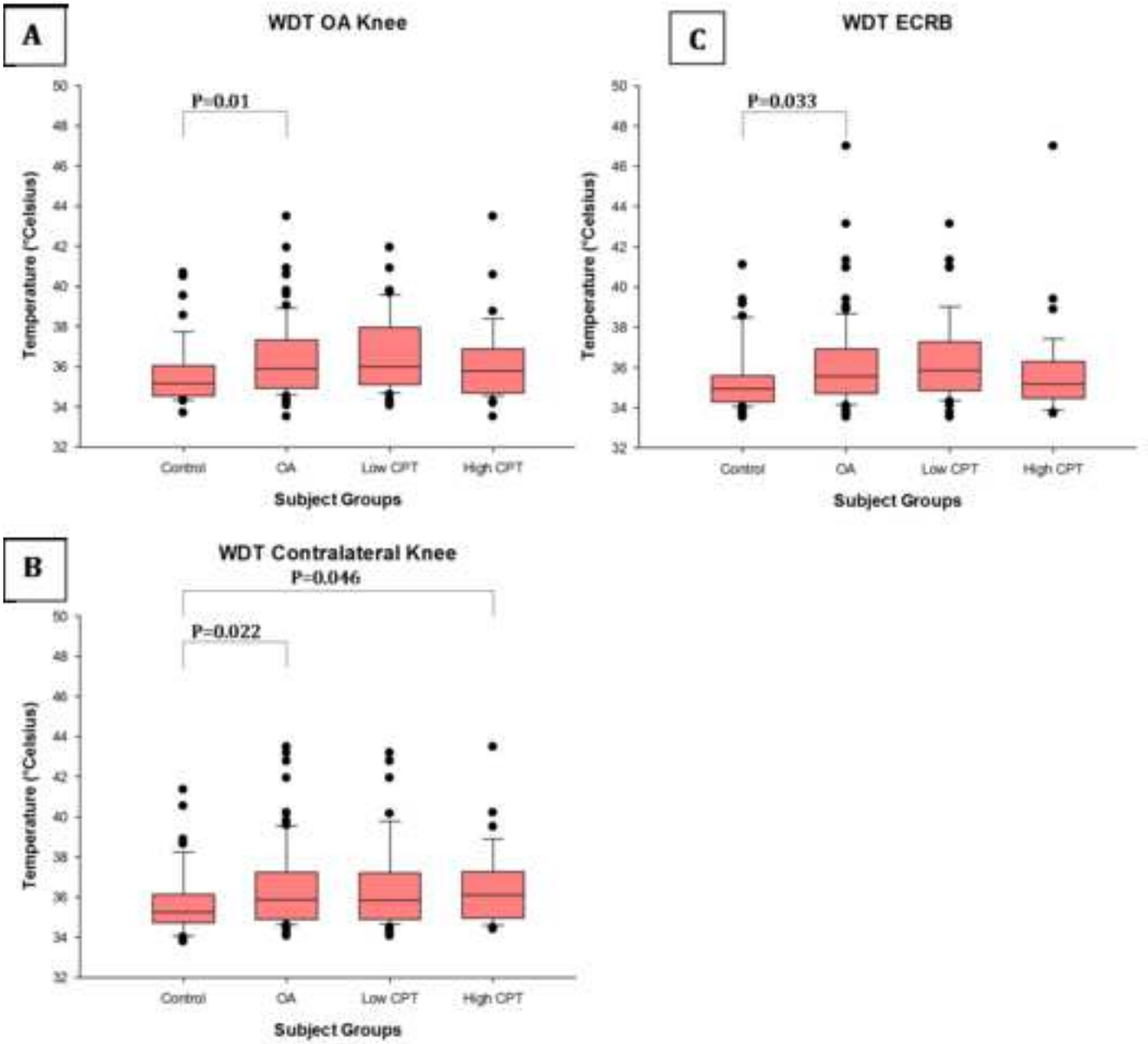

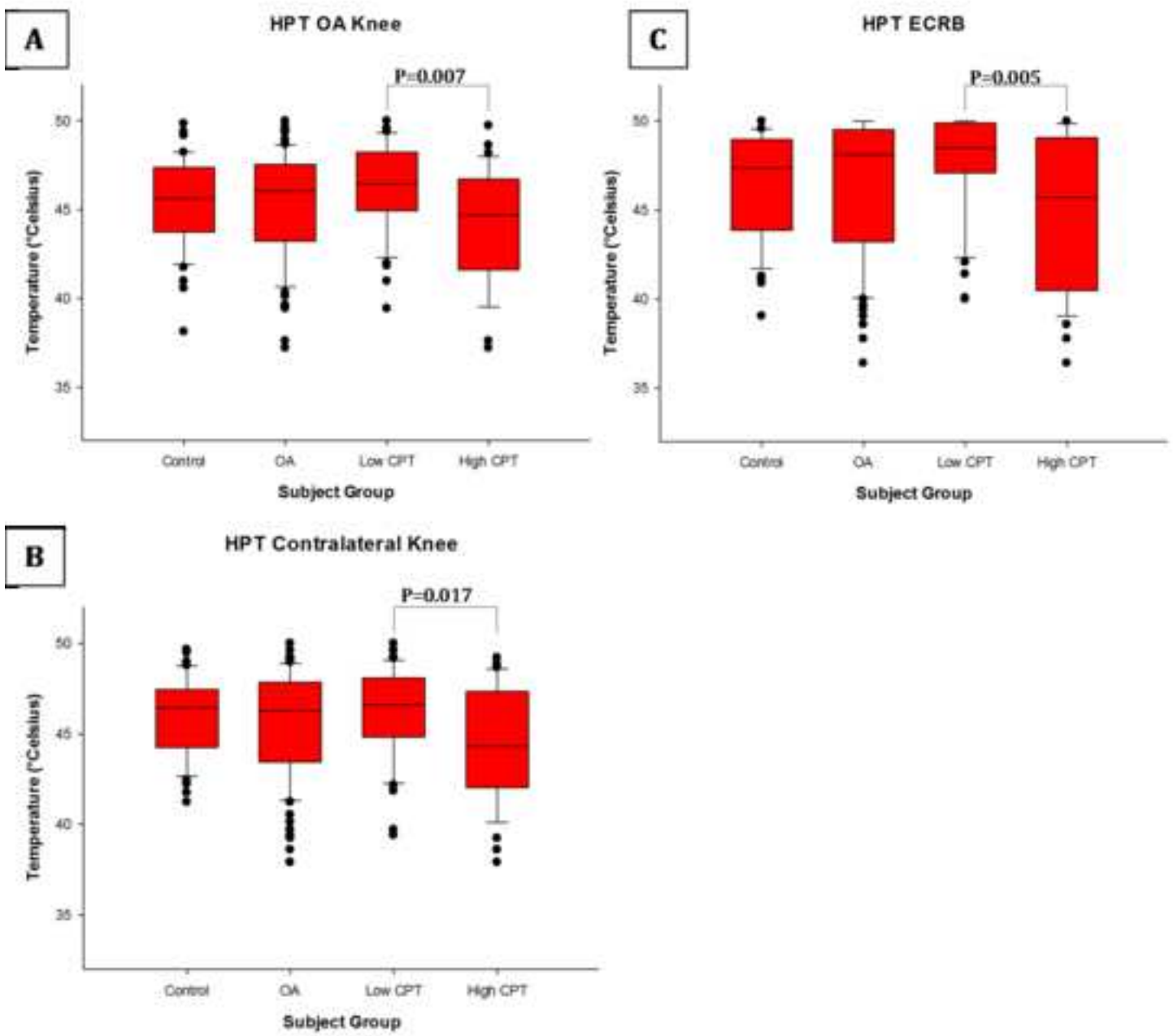

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